Medical Hypotheses 83 (2014) 668–672

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Acidic pH derived from cancer cells may induce failed reprogramming of normal differentiated cells adjacent tumor cells and turn them into cancer cells

Shima Tavakol *

Razi Drug Research Center (RDRC), Iran University of Medical Sciences, Tehran, Iran
Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
Advanced Medical Sciences and Technologies Assosiation, Student's Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 23 April 2014
Accepted 23 September 2014

ABSTRACT

Background: Eelier studies demonstrated the up-regulation of some transcriptional factors such as Oct4, Nanog, Sox2 in undifferentiated cancer cells. These transcriptional regulators are up-regulated in pluripotent cells, as well and are responsible for cell reprogramming in normal cells. It might be said that normal cells adjacent tumor site are undergone of failed cell reprogramming.

Presentation of the hypothesis: Extracellular pH of cancer cell is acidic and recent studies reveal the role of acidic environment in cell reprogramming of normal cells. This hypothesis deals with the potential role of acidic pH in malignant tumor development through normal cells adjacent cancer cells. It seems that cancer cells are more intelligent and acid release from these cells is not just a by-product but also and more important reason, is a tool to up-regulate cell reprogramming markers, induce epigenetic modification and tumor progress in normal cells adjacent cancer cells. If this is correct, then it could be expected that with alkaline targeting of tumor environment, failed cell reprogramming, aberrant epigenetic modification will decrease in normal cells adjacent cancer cells and afterward metastasis will decrease.

Testing the hypothesis: It is proposed to investigate altered genetic and epigenetic modification (DNA methylation, histone modification) in cancer, early cancer and cells in vicinity of cancer cells at different pH range of 5.8–7.8. This study is performed to determine whether acidic pH induces reprogramming, global hypomethylation and promoter hypermethylation in cancer cells and cells in vicinity of cancer cells at different pH values.

Implications of the hypothesis: This hypothesis deal with the ability of acidic pH to convert normal cells adjacent cancer cells to cancerous cells and its inductive potential on genetic and epigenetic modification of normal cells adjacent cancer cells and will further emphasize the important of extracellular acidic targeting in cancer therapy.

Background

Cancer is one of the most major causes of death worldwide. It has done a lot of efforts to cure it and increase the patient survival and it has been demonstrated a lot of mechanisms involve in. To improve survival of patient, it is noticeable to elucidate the exact mechanisms that control tumor initiating and development.

Cancer stem cells have been identified in many malignant solid tumors [1–4]. The most cancer cells overexpress Oct4 and some of them Sox-2 and these genes are overexpressed in pluripotent cells [5,6]. Cancer cells overexpress higher level of Nanog and Oct4 as compared to normal cells and lower than induced pluripotent cells (iPS). However, up-regulation of Nanog and Oct4 are in good agreement with tumorogensis, malignancy and metastasis in poorly undifferentiated tumors [7–13]. Thus, cancer is an obvious case of pathological reprogramming [14,15].

For the first time, Yamanaka et al. investigated reprogramming of fibroblast cells via plasmid gene of Oct4, Sox2, Klf4 and C-Myc [16,17] and then, it was demonstrated by other scientist [18–21]. Later, it was optimized via non-coding RNA of Oct4, Sox2 and Nanog and they revert somatic differentiated cells towards iPS [22]. However, other studies showed that knockdown of Oct4 and Nanog genes of cancer cells significantly decreased their drug resistance, tumorigenicity and metastasis [6,12]. Some studies indicated that reprogramming of cancer cells via these genes plus

* Address: Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran 1417755469, Iran. Tel.:+98 21 88992117, +98 21 88992118, +98 93 84940462.
E-mail address: sh_tavakol@razi.tums.ac.ir

http://dx.doi.org/10.1016/j.mehy.2014.09.014
0306-9877/

Nanog and Lin28 invert them towards normal phenotype and reduce drug resistance and their tumorigenicity, and this mechanism might be helpful in cancer treatment. The most important note is that iPS derived from cancer cells need c-myc for reprogramming [23,24]. Replacement of L-Myc and Glis 1 instead of C-Myc, decreases risk of tumorogensis in iPS-derived chimeric mice [25,26]. Before activation of the pluripotency regulators, C-myc activates and in partially reprogramming, self-renewal and maintenance genes are more overexpressed than pluripotency ones, and the lineage-specific transcription factors will not been completely supressed [26]. Based on this data, failed or partially cell reprogramming occurs in cancer cells and this hypothesis suggests one of the most important causes of this event.

iPS has some similarities to cancer cells same as self-renewing, high proliferative activity, domination of glycolysis metabolism [27,29], expression of pluripotency transcriptional regulators [8], alteration in gene methylation pattern and high telomerase activity [27].

The first trigger of cancer starting has not been clearly demonstrated, however genetic and epigenetic dysregulation (global DNA hypomethylation, promoter hypermethylation and histone modification) [28–30], inflammation [31–33] have been widely accepted for tumor development.

Early studies indicated that interacellular pH of cancer cells is neutral to alkaline [34,35] that sustain cytotoxicity resistance [36,37] and extracellular pH is more acidic than healthy tissues; sometimes, in metastases the pH drops to 6.0 and even 5.8 and almost, tumor size is in good agreement with decrease in pH [27,38–41]. The low extracellular pH exhibits chemoresistance and increase rate of proliferation [27,35].

Acidic pH makes stress condition for normal cells. Oct4 overexpress in stress response [7] and it can reprogram cells to pluripotency behavior. Beside, since acidic pH around 5.4–5.8 can reprogram cells and induces up-regulation of Oct4, Sox2 [42], it may act as a trigger for tumor progress. However, based on epigenetic modification derived from acidic pH, its reprogramming will not be completed and will induce cancer phenotype.

In this paper, the author subsequently proposed a hypothesis that acidic pH derived from cancer cells might induce premature termination of reprogramming and rather failed reprogramming of normal cells adjacent cancer cells and development of metastasis and malignancy in solid tumors.

Presentation of the hypothesis

As mentioned above, extracellular pH of cancer cell is acidic; sometimes, in metastases the pH drops to 6.0 and even 5.7 and it is due to altered metabolism of tumor cell towards glycolysis and high activity of some ion/proton pumps such as V-ATPase in cancer cells [43]. Although, low extracellular pH is favorable for cancer progress and proliferation but low intracellular pH triggers apoptosis via caspase cascade pathway [37,44] and less important mitochondrial membrane depolarization [45]. Interestingly, studies showed that alkalinisation of extracellular environment decreases tumor progress and metastasis [39,46] and HIF2α [38]. Recent study indicated that acidic environment induces cell reprogramming. Reprogramming of stimulus-triggered acquisition of pluripotency cells (STAP) occurs at pH of 5.4–5.8 [42]. The author proposed that acidic pH present in solid tumors may be a key factor for up-regulation of cell reprogramming markers and may induce premature termination of reprogramming in normal cell surrounded cancer cells via epigenetic modification that is resulted in tumor progress. It means that acidic pH not only affects cancer cells but also via genetic and epigenetic modification influences normal cells adjacent cancer cells and progress tumor (Fig. 1).

Acidic pH through the lactate dehydrogenase (LDH) release – as a by-product of glycolysis and transcriptional target of oncogenic signalling – up-regulates oncogenic genes such as C-Myc. C-Myc through PI3K/AKT signalling increases activity of HIF-1 and this factor induces glycolysis [47]. Notable that LDH release via this pathway maintains extracellular tumor in the range of acidic pH.

Paolo et al. indicated that methylation pattern and rather epigenetic regulation will determine failed or successful cell reprogramming fate [48].Ohnishi et al. demonstrated that transient and forced expression of Oct3/4, Klf4, Sox2, and C-Myc exhibit DNA methylation changes and tumor development in vivo [24]. Since, acidic pH up-regulates reprogramming genes, so acidic pH may involve in aberrant reprogramming via epigenetic modification in normal cells adjacent cancer cells.

Besides, C-Myc binds to H3K4me histone and exhibits epigenetic modification. However, histone methylation pattern is not permissive to bind with Oct4, sox2 and Klf4 [49,50]. Cancer cells have stable epigenetic regulations and this is significant difference between reprogramming of cancer cells with healthy ones [51].

Hjelmeland et al. demonstrated that acidic pH induces HIF2α and Glioblastoma growth [38]. On the other hand, acidic pH derived from cancer cells up-regulates HIF2α as a specific target genes same as Oct4 [52,53]. HIFα promotes transcription of important stem cell factors through epigenetic modifications and induce the histone demethylases (Jumonji family) to promote chromatin modification and tumor growth [54–57]. Chromosomal translocation count in modification of histone genes-epigenetic modification – is very fast oncogenic event [58,59]. It is noticeable that the effect of low pH is independent of hypoxia in tumor microenvironment and acidic pH can affect cells independent of HIF factors [45]. As well as the effect of acidic pH through HIF factors, it can directly affect p53 conformation and turn p53 structure into molten globule. This form is dysfunctional structure of p53 and is resulted in decrease of apoptosis in cells faced to acidic pH [60] and increase rate of proliferation in mutation-bear cells and tumor progress.

It is demonstrated that the level of extracellular LDH and acidic pH significantly increases intracellular ROS production [61] and afterward, ROS induces methylation of CpG island in promoter of miR-199a/125b, E-cadherin and catalase genes. These up-regulate ERBB2 or ERBB3 and down-regulate E-cadherin and catalase, respectively that are resulted in silencing of DNA repair transcription gene, DNA damage, tumor progress, metastasis and poor prognosis [62–64].

In this sense, it can be hypothesized that acidic pH derived from cancer cells induces epigenetic modification and premature termination of reprogramming and rather failed reprogramming of normal cells adjacent cancer cells and promote tumor and metastasis.

Testing the hypothesis

The understanding the rule of acidic pH in failed reprogramming and epigenetic modification of normal cells surrounded cancer cells and early cancer cells requires the investigation of the altered genetic and epigenetic factors that are essential to the reprogramming, proliferation and metastasis in cancer cells and cells that are in close proximity to cancer cells in range of pH between 5.8 and 7.8 in vitro and in vivo.

To adjust an acidic extracellular pH, 2-(N-morpholino)-ethanesulfonic acid and tris-(hydroxymethyl)-aminomethane [65] and or citrate-based acidic medium can applied.

Proton–Electron Double-Resonance Imaging and P magnetic resonance spectroscopy (MRS) can be applied to non-invasively measure extracellular and intracellular pH of cancer, early cancer

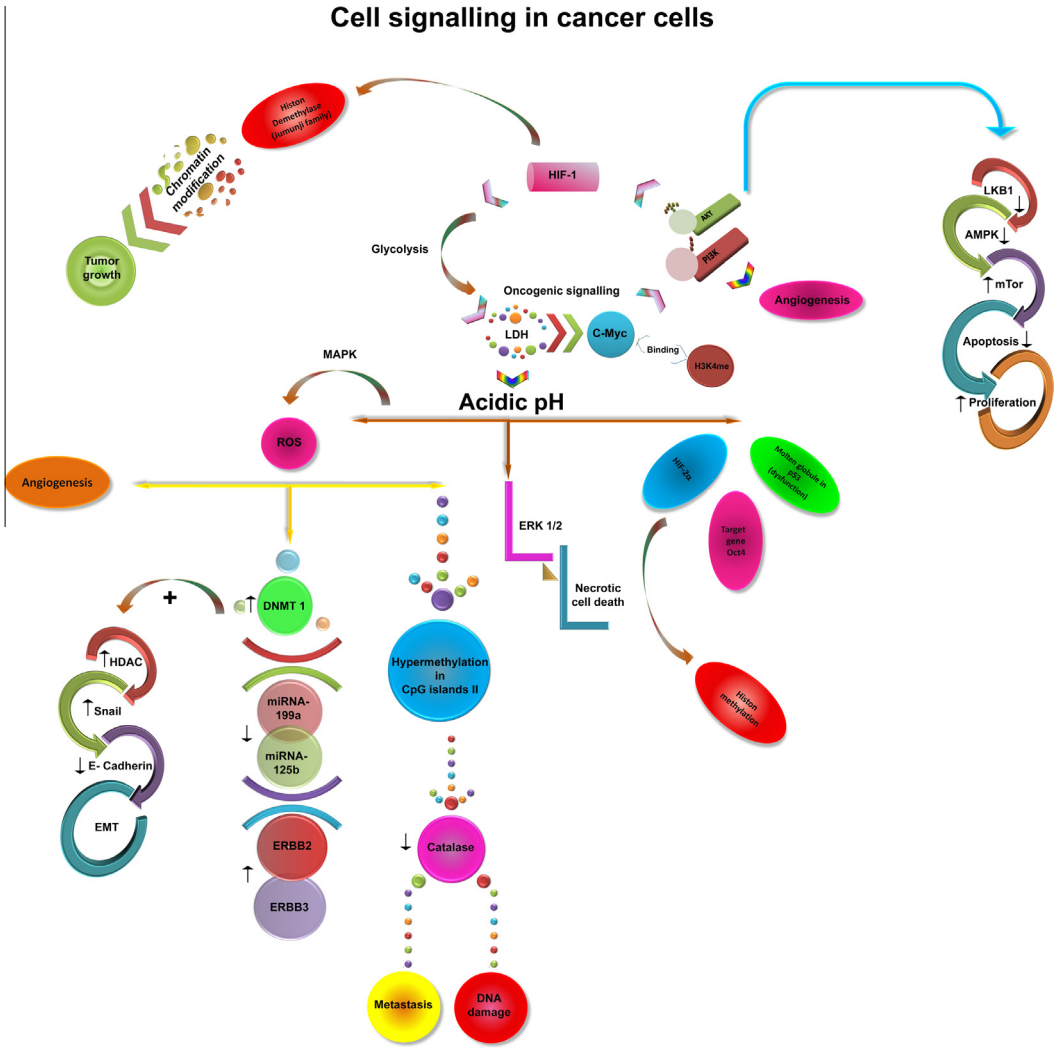

Fig. 1. Genetic and epigenetic modification in cells via acidic pH. LDH induce over expression of C-Myc and afterwards, it up-regulates HIF-1α and induces the Jumonji family of histone demethylases [54–57] and makes epigenetic modification. HIF-1 α with positive regulation induces LDH production. LDH as a source of acidic pH, up-regulates HIF2α-specific target genes same as Oct4-[52,53] and promotes chromatin modification and tumor growth. Besides, acidic pH changes conformation of p53 to molten globule, this structure is dysfunction and apoptosis is suppressed. Acidic pH through MAP kinase (MAPK) induces ROS and it up-regulates DNA methyl transfer 1 (DNMT-1) [71,72] and along with histone deacetylase (HDAC) through promoter hypermethylation supress tumor suppressor and epithelial markers and progress tumor and metastasis.

and cells in vicinity of cancer cells at different pH range of 5.8–7.8 in-vivo [40,66].

Based on genetic approach, early cancer cells and cells in near proximity of cancer cells up-regulate reprogramming genes such as Oct-4, C-Myc, SOX2, Nanog dependent on proton concentration in extracellular environment. Besides, since epithelial–mesenchymal transition (EMT) is associated with cancer malignancy and metastasis, mRNA and protein level of epithelial markers such as E-cadherin and Cytokeratin 18, and the mesenchymal markers such as Slung, Snail, Vimentin and N-cadherin and reprogramming markers containing Oct-4, C-Myc, SOX2, Nanog, Flk1 is suggested to assess at a pH range of between 5.8 and 7.8 via real-time PCR and Western-blot and flow-cytometry, respectively. It is expected that all genes and proteins except epithelial markers are up-regulated gradually in a decreasing pH manner.

Base on epigenetic approach, methylation-specific polymerase chain reaction (MSP), high performance liquid chromatography (HPLC), EMT ChIP PCR Array (histone modification) EMT DNA Methylation PCR Array (DNA methylation) are performed to determine the respective percentages of genomic C methylated in normal, cancer, early cancer and cells surrounded cancer cells at different pH range of 5.8–7.8 [67]. Since, global genomic hypomethylation is an important cause of aberrant reprogramming, it is expected that m^5C contents decrease gradually with decrease of pH.

Restriction landmark genomic scanning (RLGS) of NotI/EcoRV fragments is performed to investigate methylation in CpG islands [67].

Implications of the hypothesis

Since, decrease of oct-4 level in tumor cells increases tumor cell apoptosis, neutralizing of the tumor microenvironment will increase apoptosis via Oct4/Tcl1/Akt1 pathway [68], Stat3/survival pathway [69] or the Trp53 pathway [70] and decrease of wrong differentiation and reprogramming program in cells surrounded cancer cells. The confirmation of this hypothesis opens another perspective to chemical cues such as acidic environment around the cancer cells as a hidden Trojan, reprogramming and aberrant epigenetic factor for normal cells surrounded cancer cells. It will be helpful in the field of cancer therapy and further emphasizes the importance of targeting of acidic microenvironment.

Conclusion

Extracellular acidic pH of tumor tissue is by-product of cancer cells and studies showed that is in concordance with tumor progress. In this sense this hypothesis dealing with acidic pH present in solid tumors may be a key factor to induce up-regulation of cell reprogramming markers and epigenetic modification in normal cells adjacent tumor cells. Information from cancer signalling and epigenetic modification derived from acidic pH suggests that acidic pH derived from cancer cells can induce failed reprogramming and tumor progress in normal cells surrounded cancer cells.

Competing interests

The author declares that they have no competing interests.

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